UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,280	03/10/2004	Michele Cargill	CL1510ORD	9662

37492 7590 09/10/2007

CELERA DIAGNOSTICS, LLC
1401 HARBOR DAY PARKWAY
ALAMEDA, CA 94502

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
09/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Supplemental *Office Action Summary*	Application No. 10/796,280	Applicant(s) CARGILL ET AL.	
	Examiner Jeanine A. Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/7/06; 1/5/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,21,22 and 25-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,21,22 and 25-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/10/4* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

SUPPLEMENTAL

DETAILED ACTION

1. This is a supplemental FINAL rejection in view of the missing text within the rejections.

2. This action is in response to the papers filed November 7, 2006 and January 5, 2007. Currently, claims 1, 6, 21-22, 25-37 are pending.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

4. Any objections and rejections not reiterated below are hereby withdrawn.

a. The description rejection has been overcome by the amendments to the claims which require the polymorphism at position 101 of SEQ ID NO: 19350.

Maintained Rejections

Priority

5. This application claims priority to provisional applications 60/453,050 filed March 10, 2003 and 60/466437, filed April 30, 2003.

Drawings

6. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 21-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-6, 21-22, and newly added 25-37 are drawn to a method for identifying a human who has an altered risk for developing coronary stenosis by detecting a SNP at position 101 in SEQ ID NO: 19350 in said humans nucleic acids wherein the presence of an A at position 101 indicates a decreased risk of developing coronary stenosis and the presence of a G indicates an increased risk of developing coronary stenosis.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches polymorphisms in Apolipoproteins which are not associated with severe aortic valve stenosis. APOA, AK38, plasminogen gene are all synonyms of LPA which the instant polymorphisms lies within. Avakian et al. (Clinical Genetics, Vol. 60, pages 381-384, 2001) teaches a G/A polymorphism APO A1 which is not significantly associated with AS (see Table 3). Thus, it is clear that not all polymorphisms in the gene APO A1 is associated with each stenosis.

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic

polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that any polymorphisms within SEQ ID NO: 19,350 is associated with any risk for any stenosis in any individual.

The specification does not provide guidance for any altered risk for the SNP at position 101 of 19,350. The specification teaches hCV2590271, SEQ ID NO: 19,350 was analyzed in S0012 and V0002 samples. As seen in Table 7, page 5, the hCV25930271 is not significantly associated with coronary stenosis in the second population (p-value 0.41193). It is thus unpredictable whether the SNP is predictably associated with stenosis given the unpredictable association in two different stenosis populations. The specification teaches there is an association between the SNP and coronary stenosis in population 1. However, it is unpredictable given the varying statistical data provided in the specification whether the skilled artisan could make and use the instant invention without further unpredictable and undue experimentation.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, it is unpredictable any polymorphisms is associated with altered risk any stenosis in any individual. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it

is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts applicants have provided sufficient data analysis in the examples that the SNP at issue has been associated with coronary stenosis. The response provides that applicants have performed additional post-filing genotyping experiments using the *same two sample sets* confirming the SNP is indeed associated with coronary stenosis. This argument has been considered but is not convincing.

As provided in MPEP 716.02(g), evidence of publications post filing is not acceptable absent presentation in declaration form. Specifically, "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are probative. Here, the post-filing experiments are not in declaration form.

Further, it is unclear, if the same sample sets are used to study the same genotype, how different values for association studies may be obtained. The results provided in the specification, Table 7, illustrates for sample set S0012 a p-value of 0.03416 was obtained. The data provided in the response claims the p-value is 0.010.

If the same sample of people was studied for the same genotype it is entirely unpredictable why different results would be obtained.

More significantly, in the specification, the V0002 sample set had a p-value of 0.41193, but in the response has a p-value of less than 0.001. The response provides no explanation for the significantly different results.

Neither the specification nor the response specifically addresses the concept of heterozygote individuals and homozygosity. The Table 7 merely states the frequencies of T allele. The specification appears to teach that the presence of a T allele is significantly associated in population S0012, but not in population V0002. The detection of a T or complementary A allele would thus encompass both heterozygotes and homzygotes with either an AA or AG. Thus, the mere detection of a G or complementary C allele at position 101 would not necessarily indicate an increased risk of coronary stenosis since the specification appears to include these individuals in the analysis of the A allele. If a person is a heterozygote with a GA genotype, it is unclear how the person may be at both an increased and a decreased risk for coronary stenosis. Thus, the newly added limitations that the presence of a G indicates an increased risk of developing coronary stenosis does not appear to be supported by the instant specification.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

New Matter

8. Claims 1, 6, 25-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "the presence of G at position 101 of SEQ ID NO: 19350 indicates that the human is at an increased risk of developing coronary stenosis" are included. The amendment proposes that Table 7 supports the new claim language. However, the specification does not describe or discuss "the presence of G at position 101 of SEQ ID NO: 19350 indicates that the human is at an increased risk of developing coronary stenosis". Instead the specification illustrates in Table 7, page 5, lines 5-6, a T at the marker. Moreover, the specification describes a T is found in higher percentages of controls than in cases. This would appear to suggest that the T actually indicates a decreased risk of developing stenosis. This description does not support the presence of G at position 101 of SEQ ID NO: 19350 indicates that the human is at an increased risk of developing coronary stenosis. The concept of "the presence of G at position 101 of SEQ ID NO: 19350 indicates that the human is at an increased risk of developing coronary stenosis" does not appear to be part of the originally filed invention. Therefore, "the presence of G at position 101 of SEQ ID NO: 19350 indicates that the human is at an increased risk of developing coronary stenosis" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over rs3798220, August 12, 2002 in view of Nollau et al. (Clinical Chemistry, Vol. 43, No. 7, pages- 1114-1128, 1997).

The claims have been amended to require position 101 of SEQ ID NO: 19350 which the response asserts is also known as rs 3798220.

Rs2798220 teaches a SNP at position 101 of SEQ ID NO: 19350.

The entry in dBSNP does not specifically teach detecting a SNP by hybridization detection.

However, the ordinary artisan would have been motivated at the time the invention was made to detect known SNPs in the dbSNP database using any of the known methodologies for SNP detection to further characterize and analyze the SNP.

Nollau teaches numerous methods for detection of SNPs for further analysis and studies. Nollau teaches an overview of current methods for the detection of point mutations in clinical diagnosis.

Therefore, it would have been prima facie obvious at the time the invention was made to have detected the known SNP rs3798220 using well established SNP detection methods reviewed by Nollau for the expected benefit of analysis of the SNP for diagnostics and further characterization.

Conclusion

10. No claims allowable.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg
Primary Examiner
August 27, 2007